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U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES

PA-9947

DESIGNATED/ELECTED OFFICE (DO/EO/US)

U.S. APPLICATION NO (IF KNOWN, SEE 37 CFR

CONCERNING A FILING UNDER 35 U.S.C. 371

To be assigned 10/069691

INTERNATIONAL APPLICATION NO.

PCT/GB00/03374

INTERNATIONAL FILING DATE

September 1, 2000

PRIORITY DATE CLAIMED

September 3, 1999

TITLE OF INVENTION

Improved Container Composition for Radiopharmaceutical Agents

APPLICANT(S) FOR DO/EO/US

Stephen Gill and Stanley Francis Rushowski

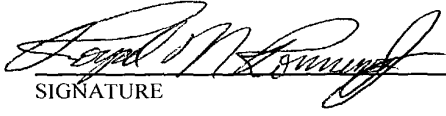
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☒ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☒ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☐ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made, however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information

copy of this transmittal letter for charging purposes
return postcard

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.492(a)(1)) To be assigned		INTERNATIONAL APPLICATION NO. PCT/GB00/03374		ATTORNEY'S DOCKET NUMBER PA-9947	
24. The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) : <input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report prepared by the EPO or JPO \$1040.00 <input checked="" type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$890.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$740.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00 ENTER APPROPRIATE BASIC FEE AMOUNT =				CALCULATIONS PTO USE ONLY	
Surcharge of \$130.00 for furnishing the oath or declaration later than _____ months from the earliest claimed priority date (37 CFR 1.492 (e)). <input type="checkbox"/> 20 <input type="checkbox"/> 30				\$890.00	
				\$0.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	14 - 20 =	0	x \$18.00	\$0.00	
Independent claims	4 - 3 =	1	x \$84.00	\$84.00	
Multiple Dependent Claims (check if applicable).			<input type="checkbox"/>	\$0.00	
TOTAL OF ABOVE CALCULATIONS =				\$974.00	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				\$0.00	
SUBTOTAL =				\$974.00	
Processing fee of \$130.00 for furnishing the English translation later than _____ months from the earliest claimed priority date (37 CFR 1.492 (f)). <input type="checkbox"/> 20 <input type="checkbox"/> 30 +				\$0.00	
TOTAL NATIONAL FEE =				\$974.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable).			<input type="checkbox"/>	\$0.00	
TOTAL FEES ENCLOSED =				\$974.00	
				Amount to be refunded	\$
				charged	\$
a. <input type="checkbox"/> A check in the amount of _____ to cover the above fees is enclosed. b. <input checked="" type="checkbox"/> Please charge my Deposit Account No. <u>500-588</u> in the amount of <u>\$974.00</u> to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>500-588</u> . A duplicate copy of this sheet is enclosed. d. <input type="checkbox"/> Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO:					
Royal N. Ronning, Jr. Amersham Biosciences Corp. 800 Centennial Avenue Piscataway, New Jersey 08855 (732) 457-8423			 SIGNATURE		
			Royal N. Ronning, Jr.		
			NAME		
			32,529		
			REGISTRATION NUMBER		
			February 21, 2002		
			DATE		

10069691 10/069691

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PA-9947

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: S. Gill, et al. Group Art Unit: To be assigned
Serial Number: To be assigned Examiner: To be assigned
Filing Date: To be assigned
Title: Improved Container Composition for Radiopharmaceutical Agents

First Preliminary Amendment

Honorable Assistant Commissioner of Patents
Box Patent Application
Washington, D.C. 20231

Sir:

Please consider the following amendments and remarks in connection with the prosecution of the captioned application, which is a filing under 35 U.S.C. § 371 and claims priority to international application number PCT/GB00/03374 filed September 1, 2000. This application also claims priority to patent application number 9920772.2 filed in Great Britain on September 3, 1999.

In the Claims

Please amend page 19, line 1, as follows:

[Claims]

What is claimed is:

Please amend claim 1 as follows:

1. (once amended) [A]In a composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface, [characterised in that] the improvement comprising the radiopharmaceutical [is]includes a metal complex.

Please amend claim 2 as follows:

2. (once amended) The composition of claim 1 [where]wherein the radiopharmaceutical is a liquid or solution.

Please amend claim 3 as follows:

3. (once amended) The composition of [claims 1 or 2 where]claim 1 wherein the metal of the metal complex is ^{111}In or $^{99\text{m}}\text{Tc}$.

Please amend claim 4 as follows:

4. (once amended) The composition of claim 1 [to 3 where]wherein the silica coating is deposited by a PCVD process.

Please amend claim 5 as follows:

5. (once amended) The composition of [claims 1 to 4 where]claim 1 wherein the container is a glass vial with a closure.

Please amend claim 7 as follows:

7. (once amended) The kit of claim 6 [where]wherein the metal complex is a ^{99m}Tc complex.

Please amend claim 8 as follows:

8. (once amended) The kit of [claims 6 or 7 where]claim 6 wherein the non-radioactive organic ligand composition is lyophilised.

Please amend claim 9 as follows:

9. (once amended) The kit of [claims 6 to 8 where]claim 6 wherein the silica coating is deposited by a PCVD process.

Please amend claim 12 as follows:

12. (once amended) The composition of claim 11, [where]wherein the bacteriostat comprises a paraben.

Please amend claim 13 as follows:

13. (once amended) The composition of [claims 10 to 12, where]claim 10 wherein the metal of the metal complex is ^{111}In or $^{99\text{m}}\text{Tc}$.

Please amend claim 14 as follows:

14. (once amended) The composition of [claims 10 to 13, where]claim 10 wherein the silica coating is deposited by a PCVD process.

In the Abstract

Please add the following abstract on a separate sheet:

-- Abstract

The present invention relates to improved radiopharmaceutical metal complex compositions, comprising the radiopharmaceutical metal complex in a container, where

the container has an internal coating of SiO₂. The internal coating of SiO₂ is preferably deposited by a plasma chemical vapour deposition (PCVD) process. Non-radioactive kit compositions for the preparation of radiopharmaceutical metal complexes using the containers of the present invention are also described.--

Remarks

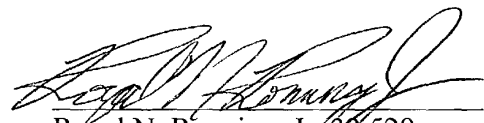
Claims 1-14 are pending in the instant application. Applicants have amended claims 1, 2, 3, 4, 5, 7, 8, 9, 12, 13, and 14 to more fully conform with U.S. practice and to delete multiple dependencies. A version of the claims marked up to show the amendments, as well as a clean version of the claims encompassing the amendments, is attached hereto.

Applicants also request that the attached abstract be added to the specification on a separate sheet as required.

Applicants respectfully assert that all amendments are fairly based on the specification, and respectfully request their entry.

Applicants believe that the claims, as amended, are in allowable form, and earnestly solicit the allowance of claims 1-14.

Respectfully submitted,



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7. (once amended) The kit of claim 6 [where]wherein the metal complex is a ^{99m}Tc complex.
8. (once amended) The kit of [claims 6 or 7 where]claim 6 wherein the non-radioactive organic ligand composition is lyophilised.
9. (once amended) The kit of [claims 6 to 8 where]claim 6 wherein the silica coating is deposited by a PCVD process.
12. (once amended) The composition of claim 11, [where]wherein the bacteriostat comprises a paraben.
13. (once amended) The composition of [claims 10 to 12, where]claim 10 wherein the metal of the metal complex is ^{111}In or ^{99m}Tc .
14. (once amended) The composition of [claims 10 to 13, where]claim 10 wherein the silica coating is deposited by a PCVD process.

Claims (clean version encompassing amendments)

What is claimed is:

1. (once amended) In a composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface, the improvement comprising the radiopharmaceutical includes a metal complex.
2. (once amended) The composition of claim 1 wherein the radiopharmaceutical is a liquid or solution.
3. (once amended) The composition of claim 1 wherein the metal of the metal complex is ^{111}In or $^{99\text{m}}\text{Tc}$.
4. (once amended) The composition of claim 1 wherein the silica coating is deposited by a PCVD process.
5. (once amended) The composition of claim 1 wherein the container is a glass vial with a closure.
6. A kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface.

7. (once amended) The kit of claim 6 wherein the metal complex is a ^{99m}Tc complex.
8. (once amended) The kit of claim 6 wherein the non-radioactive organic ligand composition is lyophilised.
9. (once amended) The kit of claim 6 wherein the silica coating is deposited by a PCVD process.
10. A composition for the preparation of a stabilised radiopharmaceutical metal complex which comprises a stabiliser suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.
11. A composition for the preparation of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.
12. (once amended) The composition of claim 11, wherein the bacteriostat comprises a paraben.
13. (once amended) The composition of claim 10 wherein the metal of the metal complex is ^{111}In or ^{99m}Tc .

14. (once amended) The composition of claim 10 wherein the silica coating is deposited by a PCVD process.

Abstract

The present invention relates to improved radiopharmaceutical metal complex compositions, comprising the radiopharmaceutical metal complex in a container, where the container has an internal coating of SiO_2 . The internal coating of SiO_2 is preferably deposited by a plasma chemical vapour deposition (PCVD) process. Non-radioactive kit compositions for the preparation of radiopharmaceutical metal complexes using the containers of the present invention are also described.

Improved Container Composition for Radiopharmaceutical AgentsSummary of the Invention

5 The present invention relates to improved containers for radiopharmaceutical metal complexes, where the container has an internal coating of silica (ie. silicon dioxide or SiO_2), preferably deposited by a plasma chemical vapour deposition (PCVD) process.

Field of the Invention

10 The present invention relates to radiopharmaceutical metal complexes, and kits for the preparation of such complexes, in a container having a silica coating on the surface(s) which are in contact with the radiopharmaceutical.

Background to the Invention

15 US 4385086 (1983) discloses that a variety of materials (eg. soda glass, ceramics and metals) can be coated with highly oxidised silicon to prevent the leaching of metal ions from the material.

20 FR 2697014 A1 (1994) discloses the silica coating of bottles, flasks, ampoules and other containers intended for use with food or liquid pharmaceutical products, to reduce leaching of metals from the container into the liquid contents of the container.

 DE 29609958 U1 discloses that glass containers having an internal coating of SiO_2 prepared by PCVD are useful for the storage of pharmaceutical or diagnostic solutions.

25

JP 11-99192A discloses that silica-coated vials (prepared by a chemical coating and pyrolysis method), are useful to prevent adsorption of radiopharmaceutical products such as ^{201}Tl solution to the surface of the glass. The silica coating of these vials is manufactured by the method described in JP 2815595 B which involves treating the glass surface with a silyl tetraisocyanate vapour in a carrier gas, followed by heating at high temperatures. JP 2815595 B also discloses that such a silica coating is useful to prevent leaching of impurities such as alkali from the glass into medical products.

Summary of the Invention

The present invention relates to silica-coated containers in combination with the following categories of products:

- (i) radioactive radiopharmaceutical products which are metal complexes,
- (ii) lyophilised non-radioactive kits for the preparation of radiopharmaceutical metal complexes, especially for the preparation of $^{99\text{m}}\text{Tc}$ radiopharmaceuticals.

Detailed Description of the Invention

The present invention relates to a composition comprising a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface. The present invention also relates to non-radioactive, preferably lyophilised kits for the preparation of radiopharmaceutical metal complexes, where the kit composition is supplied in a container which has a silica coating on the inner surface.

Suitable silica-coated containers for use in the present invention are commercially available, e.g. a silica-coated vial called Silicoat is available from Fuji Glass KK, and a silica-coated vial called Type I Plus is available from Schott Glas. The Type I Plus vial is prepared by a plasma chemical vapour deposition (PCVD) process.

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Other containers can be coated with silica using known methods, where the silicon-containing layer is deposited from either gas phase or liquid phase contact with the container surface(s), with optional pyrolysis and/or oxidation to convert the deposited silicon-containing layer to SiO_2 . Such methods are known in the art. Using either approach, irregularly-shaped containers can be coated. Examples of gas phase deposition are PCVD, and the process of JP 2815595 B which uses silyl tetraisocyanate vapour in carrier gas. The latter process delivers the silicon-containing layer in a single step, with pyrolysis of silyl tetraisocyanate required to give the final product, i.e. the coated vial. Depending on the efficiency of the heat transfer, the coating layer may not be pure SiO_2 , but perhaps contain carbon or nitrogen. The silica-coated vial prepared by PCVD has advantages over the disclosures of JP 2815595 B and JP 11-99192A, because the SiO_2 layer prepared by PCVD is in fact developed by multiple exposure to the vapour phase silicon reagent. The result is a much more uniform layer of high purity SiO_2 , which is mechanically sound and resistant to abrasion etc. Hence PCVD is a preferred process for use in containers of the present invention.

20

The term "metal complex" as used herein means a coordination complex of a metal (M) with an organic ligand (L). This is to be contrasted with an uncomplexed or free metal ion e.g. the monovalent thallium cation Tl^+ . The term 'organic ligand' as used herein means a carbon-containing compound which comprises at least one heteroatom suitable for

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coordination to a metal, such as N, O, S, P or Se, or combinations thereof. Examples of organic ligands are amines, hydrazines (eg. hydrazinonicotinamide or HYNIC), ethers such as crown ethers, thiols or thioethers, oximes, isonitriles (eg. sestamibi), phosphines, amides, pyridines or other heterocyclic molecules such as quinolines. Multiple metal donor atoms can be arranged together to form chelating agents or polydentate ligands such as:

- diaminedioximes such as propyleneamineoxime (ie. PnAO), or hexamethylpropyleneamineoxime (ie. HMPAO), or analogues thereof;
- hydroxyquinolines;
- N₂S₂ ligands such as diaminedithiols (eg. ethylcysteineate dimer or ECD, ie. bicesate), diamidedithiols or amideaminedithiols;
- N₃S ligands such as thioltriamides (eg. mercaptoacetyltriglycine or MAG3);
- diphosphines (eg. tetrofosmin);
- dithiols (eg. dimercaptosuccinic acid or DMSA);
- aminocarboxylate ligands (eg. EDTA or DTPA);

and many more combinations as are well known in the art.

If leached metal ions M' (such as aluminium or sodium), leach from glass into a chemical product which is a radiopharmaceutical metal complex of a radiometal M, these leached metal ions may adversely affect the product in a manner which goes beyond the simple presence of M' as an impurity:

- (i) $ML_n + M' \rightarrow M'L_q + M$ ligand exchange or transmetallation
(ii) $L + M' \rightarrow M'L_q$ complexation

5 where:

M is the radiometal of the desired radiopharmaceutical product,

L is the organic ligand;

M' is the leached metal ion;

10 ML_n is the metal complex radiopharmaceutical product, which may
comprise 2 or more different organic ligands L;

n is number of ligands (L) attached to M and is an integer of value 1 to 8;

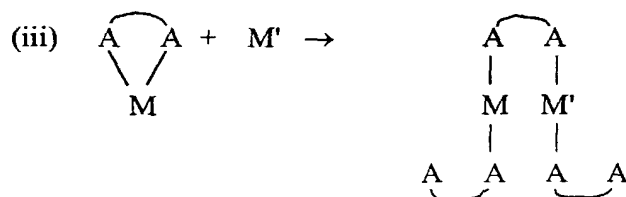
$M'L_q$ is the metal complex impurity;

q is number of ligands (L) attached to M' and is an integer of value 1 to 8.

15 Process (i) can occur when the leached metal or metals (M') have greater affinity for one or
more of the organic ligands (L) than the radiometal (M) of the radiopharmaceutical
product. For a radioactive product, ML_n is the radiopharmaceutical and could be e.g.
 $^{111}\text{In}(\text{oxine})_3$ where M is ^{111}In and oxine is 8-hydroxyquinoline, or the $^{99\text{m}}\text{Tc}$ complex of
DMSA (dimercaptosuccinic acid). It is important to recognise that, for radiopharmaceutical
20 products, ML_n is present at extremely low (typically nanomolar or picomolar)
concentrations. Consequently, even low levels of leached metal ions (M') from the glass,
can have a significant effect on the radiochemical purity of the ML_n product, by increasing
the levels of free radiometal (M) impurity. Such free radiometal could then generate
further radioactive impurities by undergoing e.g. redox reactions, or complexation with
25 other available ligands.

In addition to, or instead of equation (i), complexation (ii) may also occur. This leads to the presence of undesirable $M'L_q$ impurities in the product ML_n . $M'L_q$ is non-radioactive, but for a radiopharmaceutical agent, the ligand (L) is usually present in vast chemical excess over the metal (M) present, hence if M' has any affinity for L, equation (ii) is always likely to occur. $M'L_q$ may be insoluble in the medium present in the radiopharmaceutical vial or container, and may thus tend to precipitate. This may potentially promote co-precipitation of the desired species ML_n , and hence introduce yet further potential radioactive impurities.

When L is a multidentate ligand, such as a chelating agent the number of metal donor sites (A) per ligand (L) may be 2, 3, 4, 5, 6 or 8 typically. In that case, a process which is a special case of equation (i) above could occur as follows:



where: the free A donors can complex to further M/ M' atoms etc.

note: the curved lines represent the chain of atoms linking the A groups.

leading to dimeric or oligomeric binuclear or polynuclear metal complexes involving both radiometal M and non-radioactive metal M' . The leached metal (M') may be less amenable to chelation by polydentate ligand (L), and hence favour such polynuclear species, even when M does not. This would result when the energetics are less favourable, e.g. M' is too small for two A groups to coordinate without undue steric interactions from either the A

groups themselves, or the ligand backbone linking the A groups. Clearly, the greater the denticity of the ligand L (i.e. the greater the number of A metal donor sites), the greater the potential complexity of the impurity product.

5 In the light of the above, it can be seen that the influence of leachable metal ions (M'), can have effects which go far beyond just the presence of M' as a metal ion impurity. This is important for radiopharmaceutical metal complex products and is not recognised by JP 11-99192A, which makes no specific reference to radiopharmaceuticals which are metal complexes. The ^{201}Tl radioisotope taught by JP 11-99192 A is an uncomplexed radiometal
10 in the chemical form of the Tl(I) cation Tl^+ . The teaching of JP 11-99192 A relates only to adsorption effects *via* an ion exchange mechanism for the Tl-201 cation (ie. Tl^+) with the non-radioactive Na^+ and K^+ ions of the glass container walls. The main thrust of JP 11-99192 A is to a radiopharmaceutical vial having reversed text characters on the surface of the container

15 For uncoated glass containers, the leaching of metal ions from the glass can potentially be overcome, or at least reduced, by washing with dilute aqueous acid solutions (to remove relatively labile leachable metal ions), following by rinsing and (optionally) drying steps, before the container is charged with product. The layer of silica (SiO_2)
20 suppresses any such leaching of metal ions (M'), and hence obviates the need for any such washing steps. This simplification is particularly important for diagnostic products intended for human use such as radiopharmaceuticals, which are typically administered by injection into the human bloodstream, since these washing steps must be done in a sterile manner. Hence although such steps may be straightforward, their removal represents a
25 significant improvement.

The radiopharmaceutical product ^{111}In -oxine aqueous solution has been observed to suffer from an intermittent problem whereby, in some batches ^{111}In activity is lost to an insoluble precipitate which settles out of solution. Model experiments have identified this precipitate as a mixture of aluminium oxinate, with co-precipitated $^{111}\text{In}(\text{oxine})_3$ (see Example 2). This illustrates the fact that the leaching of metal ions, in that case aluminium, from glass can cause unforeseen problems for metal complex radiopharmaceuticals, even when the initial effect is simply to form a $\text{M}'\text{L}_q$ complex as per equation (ii) above. It will be recognised that the interaction of leached metal ions with radiopharmaceutical metal complexes at tracer concentrations could produce a variety of impurities which are difficult to predict, identify and control when the glass can function as an uncontrolled source of a variety of metal ion impurities. Consequently, elimination of the leached metal ion by use of an inert barrier layer of SiO_2 eliminates the cause of this problem. Example 1 shows that a silica-coated vial reduces the leaching of aluminium to minimal levels, and hence solves the problem referred to above for $^{111}\text{In}(\text{oxine})_3$.

Similarly, a lyophilised non-radioactive kit for the preparation of the kidney imaging agent $^{99\text{m}}\text{Tc}$ -DMSA has been found to suffer from problems of radioactive particulate impurities following reconstitution with $^{99\text{m}}\text{Tc}$ -pertechnetate ($^{99\text{m}}\text{TcO}_4^-$). The particle size of these radioactive particles is such that, once administered to the patient, the particles are retained in the liver. This represents a major problem for an agent which is intended to be used for kidney imaging. Example 4 shows that this biodistribution problem occurs when higher concentrations of aluminium ions than normal are present. Hence eliminating the leaching of aluminium from the glass vial is expected to significantly reduce or eliminate this problem. The problem with $^{99\text{m}}\text{Tc}$ -DMSA indicates

that leaching can occur even in lyophilised products which are reconstituted to give the radiopharmaceutical, i.e. that leaching can occur even when the contact time of the solution with the glass is only a matter of minutes.

5 JP 11-99192A concerns itself only with the issue of whether a free radioactive metal ion, (^{201}Tl as Tl^+), is adsorbed onto the vial walls. For a radiopharmaceutical metal complex (ML_n), the non-radioactive organic ligand L and its complex $\text{M}'\text{L}_q$ may suffer from adsorption problems. L may also potentially complex with M' ions which remain bound within the container walls to form $\text{M}'\text{L}_q$ complexes chemically bound to the glass.

10 Adsorption is particularly likely to be a problem when L and/or $\text{M}'\text{L}_q$ is not too soluble in the solution medium, e.g. a lipophilic ligand such as oxine in a predominantly aqueous medium. Such loss of ligand due to adsorption or complexation may not adversely affect the preparation of the metal complex (ML_n) *per se*, since for a radiopharmaceutical L is usually present in vast chemical excess over M. Unwarranted loss of L does, however,

15 impact on the reproducibility of manufacture of a controlled diagnostic product for human administration, since variable assay results for L are highly undesirable with respect to GMP. Example 3 demonstrates oxine ligand loss problems for an oxine ligand aqueous solution formulation, and shows that loss of oxine can occur by both the mechanisms referred to above. Silica-coated vials would eliminate loss of oxine to aluminium, and

20 would be expected to reduce the degree of adsorption. The overall effect would be a reduction in the loss of oxine ligand from the solution. Hence, for these reasons also, metal complex radiopharmaceuticals in silica-coated vials have surprising advantages compared to what is described in the prior art.

The silica-coated vial can be used in combination with other non-radioactive components of a kit for the preparation of metal complex radiopharmaceuticals apart from the organic ligand (L), e.g. stabilisers, or bacteriostats. Such stabilisers or bacteriostats may suffer from analogous problems to those described above for oxine – ie. potential
5 adsorption and/or complexation with leached metals. Bacteriostats include parabens, benzyl alcohol, cetrimide, benzoic acid, chlorbutanol, chlorocresol, cresol, phenol, benzethonium chloride and thiomersal. Some bacteriostats such as methyl paraben (ie. methyl *p*-hydroxybenzoate), or propyl paraben (propyl *p*-hydroxybenzoate) are relatively insoluble in water, and hence a silica-coated container would be expected to reduce
10 formulation problems. Also, cobalt is known as a stabiliser for the ^{99m}Tc metal complex of the ligand HMPAO (hexamethylpropyleneamine oxime) [Eur. J. Nucl. Med., 20, 661-6 (1993) P. S. Weisner *et al*], and may be supplied in a separate vial to the HMPAO ligand vial. Reduced adsorption of cobalt onto the vial walls of a silica-coated vial is shown in
15 Example 5. This shows that adsorption can occur in macroscopic amounts, not just at the tracer concentration described in the prior art for ²⁰¹Tl, and that silica-coated containers are useful for excipients used in the preparation of metal complex radiopharmaceuticals, such as stabilisers or bacteriostats.

20 Experimental

Example 1

Groups of 10 Type I Plus vials (Schott Glas) were subjected to a series of stress tests to demonstrate the robustness of the silica coating with respect to leachable ions.

The basic test was the resistance of the coating to the leaching of cations when autoclaved with 0.04M aqueous HCl. This test was performed after vials were exposed to the following stress test conditions 1 to 4:

1. Vials were washed, and then pyrogen baked. 2ml of 0.04M HCl was added and the vials sealed. Test vials were autoclaved, then stored upright at 40°C before testing for leachable cations.
2. Vials were stored for 6 weeks at -196°C, then washed and pyrogen baked. 2ml of 0.04M HCl was added to each vial, and the vials were then sealed, autoclaved and tested for leachable cations.
3. As test 2, except that the vials were stored at -70°C, -20°C, +20°C and +40°C/75% relative humidity.
4. Further tests included vials pyrogen baked 3 times, vials containing 0.04M HCl autoclaved three times, vials gamma irradiated (35.4 – 36.2 kGy dose).

All test solutions were measured by ICP for silicon, sodium, aluminium and boron, ie. those cations considered to be most leachable from the vial surface. The results are given in Table 1.

Table 1

Test Number	Si	Na	Al	B
1	0.149	Nd	0.006	Nd
2	0.163	Nd	Nd	Nd
3 -70°C	0.167	Nd	Nd	Nd
-20°C	0.193	0.005	0.002	0.002
+20°C	0.193	0.009	0.005	0.003
+40°C	0.236	0.006	0.002	0.002
4 bake	0.110	Nd	0.010	Nd
X3	0.378	0.012	Nd	0.006
Gamma	0.102	0.003	Nd	Nd

Note: each table entry is the mean of 12 batch runs, each batch of 10 vials (i.e. 120 vials tested),
 5 expressed in $\mu\text{g}/\text{cm}^3$ of test solution.

Nd = not detected. Detection limits (in $\mu\text{g}/\text{cm}^3$):

Si – 0.003

Na – 0.004

Al – 0.004

B – 0.004

10 All of the results were satisfactory, particularly for the key cations sodium and aluminium, each of which had mean values of approximately $0.01\mu\text{g}$ per ml of test solution. These very low levels demonstrate the robustness of the silica coating under
 15 stress conditions.

There were no significant differences in the results obtained between vials from different proving runs. This demonstrates the reproducibility of the silica coating process.

5

Example 2: Indium Oxine and Aluminium

A non-radioactive oxine stock solution without ^{111}In was prepared from approved reagents. The active sub-batch was prepared from the same reagents but with sufficient ^{111}In -indium chloride in 0.04 M HCl stock solution to give a reference activity of 0.1 mCi/ml.

10

For the active experiment, 10 P6 glass vials (ie. uncoated USP Type 1 glass vials) were each dispensed with 1 ml of radioactive stock solution. For the inactive experiment, approximately 390 P6 vials were each dispensed with 1 ml of oxine stock solution. All the vials were stoppered, oversealed and autoclaved in the approved manner. The active vials were subjected to RAC (radioactive concentration) determination, both initially and after standing for 1 day. The inactive vials were left for 3 days in the upright position.

15

The precipitate was harvested from the inactive P6 vials by the following procedure:

20

10 vials were decapped and decanted into a Sterilin container;

each vial was washed with 1 ml pyrogen-free water and the washings added to the Sterilin;

25

a further 10 vials were treated as above to create a second filled Sterilin;

the Sterilins were centrifuged at 2000 rpm for 10 minutes;
the supernatants were decanted and the above procedures repeated using the same
Sterilin containers;
this cycle was repeated until all the inactive vial contents had been processed
5 through the two Sterilins;
the precipitate in each Sterilin were transferred to separate tared vials and freeze-
dried;
at the completion of freeze-drying, the vials were re-weighed.

10 Results:

(i) Active vials

The P6 vials gave a mean decrease in of ^{111}In activity of 16.7% with a maximum of 38.7%.
However, some of the P6 vials had initial RACs substantially below the expected value of
15 0.1 mCi/ml. The vials with the lower initial RACs tended subsequently to show the
highest RAC drops.

(ii) Inactive vials

The processing of the inactive vials yielded a small but visible quantity of green precipitate
20 in each Sterilin. The total yield of freeze-dried precipitate was 7.0 mg. ^1H NMR and
chromatographic analysis compared with an authentic sample of aluminium oxinate
showed the precipitate to be predominantly aluminium oxinate.

Example 3: Oxine Ligand Loss

20 P6 glass vials were rinsed with water, drained and baked to depyrogenate. Each vial was then dispensed with an aqueous solution containing 50 μ g of oxine, and the oxine content determined by HPLC at various time points. The results are shown in Table 2:

Table 2: Oxine Loss by HPLC

Time Point	Oxine in Solution	Solution/ Suspension Al(ox)3	Glass oxine	Glass Al(ox)3	Recovery (%)
initial	25.2	8.5	5.1	2.3	82
reference	20.1	26.7	3.1	6.0	~100
expiry	20.3	27.7	2.5	7.3	~100
expiry +14 days	19.0	16.4	6.6	5.7	95

10 HPLC System

Column: Hamilton PRP1, 150 x 4.1mm, μ m particle size

Eluent A: 25 mM KH_2PO_4 adjusted to pH 10.3 – 10.5 with KOH

Eluent B: Acetonitrile

Gradient: 0% B $\xrightarrow{15 \text{ min}}$ 50% B $\xrightarrow{5 \text{ min}}$ 50% B $\xrightarrow{3 \text{ min}}$ 0% B

15 Flow Rate: 1.75ml/min.

Injection volume: 20 μ g

Detection: UV at 254nm, path length 10mm

System control and data processing: Gilson 715 System Controller

20 The system was calibrated using 50 μ g/ml solutions of oxine in water and aluminium oxinate in acetonitrile. Retention time of oxine was ca. 15 – 15.2 min, and Al(oxinate) ca. 17 min.

For solution/suspension measurements, samples of vial contents were taken directly and injected. The oxine and aluminium oxinate peaks were each integrated and the aluminium oxinate peak area normalised to give an oxine equivalent. The results were then scaled to give a total solution/suspension content. For measurements of oxine and aluminium oxinate adsorbed on the vial walls, the vial was decapped, drained and carefully rinsed with 0.2ml acetonitrile. 20 μ g of the rinse solution was injected, the peaks integrated and the aluminium oxinate peak area normalised to give an oxine equivalent. Previous experiments had shown oxine losses to the vial stopper to be negligible.

Example 4

Freeze-dried kits using USP Type 1 glass vials (i.e. P6 uncoated vials) containing the following formulation were prepared:

<i>meso</i> -DMSA	1.0mg
SnCl ₂ . 2H ₂ O	0.42mg
ascorbic acid	0.7mg
inositol	50.0mg

These vials were reconstituted with 0.9% saline B.P. and set aside for 1 hour. A proportion (ca. 1 in 10) of the vials were found to contain aluminium levels of up to 2 μ g/vial. Standing these vials for longer periods gave levels of up to 6 μ g/vial of aluminium.

When the above lyophilised DMSA kit formulation vials were reconstituted with ^{99m}Tc generator eluate (ie. ^{99m}Tc-pertechnetate in saline) which was known to contain 1 μ g/ml aluminium ion, the product exhibited atypical elevated liver uptake in a rat biodistribution test. The atypical behaviour was reflected in reduced kidney: liver and

Table 3: Cobalt Adsorption

Vial	Vol added (cm ³)	Cobalt content (μg/cm ³)	Statistics
Stock #1	1.997	24.58	mean = 24.31 max = 24.58 min = 23.97
#2	1.998	24.41	
#3	1.998	24.32	
#4	1.999	24.58	
#5	1.992	23.97	
#6	1.995	24.03	
P6 #1	1.976	13.87	mean = 14.61 max = 17.84 min = 12.80
#2	1.982	13.27	
#3	1.985	16.52	
#4	1.978	17.84	
#5	1.982	13.40	
#6	1.985	12.80	
coated #1	1.986	25.21	mean = 24.49 max = 25.21 min = 23.81
#2	1.975	24.86	
#3	1.979	23.81	
#4	1.983	24.82	
#5	1.987	24.40	
#6	1.983	23.87	

Claims

1. A composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface, characterised in that the radiopharmaceutical is a metal complex.

2. The composition of claim 1 where the radiopharmaceutical is a liquid or solution.

3. The composition of claims 1 or 2 where the metal of the metal complex is ^{111}In or $^{99\text{m}}\text{Tc}$.

4. The composition of claims 1 to 3 where the silica coating is deposited by a PCVD process.

5. The composition of claims 1 to 4 where the container is a glass vial with a closure.

6. A kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface.

7. The kit of claim 6 where the metal complex is a $^{99\text{m}}\text{Tc}$ complex.

8. The kit of claims 6 or 7 where the non-radioactive organic ligand composition is lyophilised.

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(57) Abstract: The present invention relates to improved radiopharmaceutical metal complex compositions, comprising the radio-
pharmaceutical metal complex in a container, where the container has an internal coating of SiO₂. The internal coating of SiO₂ is
preferably deposited by a plasma chemical vapour deposition (PCVD) process. Non-radioactive kit compositions for the preparation
of radiopharmaceutical metal complexes using the containers of the present invention are also described.

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**DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

Improved Container Composition for Radiopharmaceutical Agents

the specification of which

☐ is attached hereto.

OR

☒ was filed on September 1, 2000 as United States Application No. or PCT International Application No. PCT/GB00/03374 and was amended on _____.(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or (f) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign applications for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

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I hereby claim the benefit under 35 U.S.C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the

duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, CFR Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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